

REMARKS

Claims 6-7 are pending. Claims 6-7 are amended. The amendments are supported by the specification and the originally filed claims. In particular, claims 6-7 are amended to clarify the scope of the claims with regards to the enantiomeric excess of the (S) form. No new matter is added. Applicants respectfully request reconsideration and withdrawal of all rejections.

Claims 6-7 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Del Soldato (U.S. Patent No. 5,700,947). This rejection is traversed.

Applicants agree with the Examiner that Del Soldato discloses the compound of the present claims, which naturally includes the (S)-enantiomer. However, Applicants respectfully submit that Del Soldato does not teach or suggest the “4-nitroxybutyl ester of 2-(6-methoxy-2-naphthyl)-propanoic acid having an enantiomeric excess of the (S) form higher than or equal to 97%” (present claim 6) (emphasis added) or 98% (present claim 7). Thus, the present application provides a “selection invention” within the broader disclosure of Del Soldato.

The specification of the present invention discloses a “new method for preparing nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid (naproxene) having an enantiomeric excess of the (S) form higher than or equal to 97% ... combined with high yields” (page 1, first paragraph). “The Applicant has found surprisingly by the use of inorganic bases it is possible to improve the enantiomeric excess of naproxene nitroxyalkylesters with respect to the prior art methods, which use, as seen, organic bases, with high yields” (Specification, paragraph bridging pages 4-5) (emphasis added). See also, the process disclosed by pages 2-4 and Examples 2-6. The

specification explains that while “prior art synthesis methods of nitroxyalkylesters of the 2-(S)-(6-methoxy-2-naphthyl)-propanoic acid, are known [citing WO 98/25,918], ... [t]ests carried out by the applicant have shown that this process of the prior art does not allow to obtain naproxene nitroxyalkylesters having an enantiomeric excess in the range of 55-80% only with a specific organic base, 4-N,N-dimethylamino pyridine, 94% is obtained” (Specification, paragraph bridging pages 1-2, Example 1 and comparative Examples 7-9) (emphasis added). Thus, the prior art processes were unable to obtain the “enantiomeric excess of the (S) form higher than or equal to 97%” of the presently claimed invention (claim 6) (emphasis added).

Del Soldato does not satisfy this deficiency as Del Soldato neither teaches nor suggests the claimed enantiomeric excess of the (S) form nor a process capable of obtaining the claimed enantiomeric excess of the (S) form. For example, Del Soldato discloses obtaining the “nitric ester of 2-(6-methoxy-2-naphthyl)propionate of 4-hydroxy-butyl (V)” in Example 1 by a process, which reads as follows:

a) 0.59 g of EtONa dissolved in 10 ml of ethyl alcohol were added, by slow dripping, to a solution of 2 g of 2-(6-methoxy-2-naphthyl)propionic acid, dissolved in 20 ml of ethyl alcohol. The reaction mixture was stirred for 5 minutes at room temperature, then the solvent was evaporated at a reduced pressure, obtaining 2.1 g of sodium salt of 2-(6-methoxy-2-naphthyl)propionic acid. The 2.1 g of sodium salt of 2-(6-methoxy-2-naphthyl) propionic acid so obtained were dispersed in 40 ml of dimethylformamide and 1.5 g of 1-Br-4-Cl-butane dissolved in 30 ml of dimethylformamide were added by dripping to this dispersion. The reaction mixture was stirred for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The organic phase so extracted was anhydriified on sodium sulfate and the solvent was evaporated at a reduced pressure until a dry residue of 2 g was obtained. The residue was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v).

The head fractions were collected, the solvent was evaporated at a reduced pressure and 1 g of 2-(6-methoxy-2-naphtyl) propionate of 4-chlorobutyl (IX) was obtained.

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b) 0.79 g of AgNO₃ dissolved in 1.3 ml of acetonitrile were dripped to 1 g of (IX) obtained as described in a), dissolved in 4,5 ml of acetonitrile. The reaction mixture was stirred for 12 hours at a temperature of 85°C. and then filtered.

From the resulting solution, the solvent was evaporated at a reduced pressure, and a residue was obtained to which 10 ml of methylene chloride were added. The mix so obtained was filtered once again, the organic phase was washed with water and then anhydried on sodium sulfate. The solvent was evaporated under reduced pressure and 1.8 g of a dry residue was obtained, which was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v). The fractions containing the product were collected, the solvent was evaporated at a reduced pressure and 1.5 g of nitric ester of 2-(6-methoxy-2-naphtyl)propionate of 4-hydroxy-butyl (V) were obtained.

(Del Soldato, column 7 line 35 to column 8, line 12). The process of Example 1 does not result in the claimed enantiomeric excess of the (S) form higher or equal to 97%. Nor could one of ordinary skill in the art modify the process of Del Soldato to produce such a high enantiomeric excess. In fact, one way of producing the claimed enantiomeric excess is claimed in the granted parent of the present application. This fact proves that the process of Del Soldato could not have been used to produce such a high enantiomeric excess.


As Del Soldato does not teach or suggest the "enantiomeric excess of the (S) form higher than or equal to 97%" of claim 6, or provide any manner in which such a high enantiomeric excess could be obtained, Applicants respectfully submit that those of skill in the art would not have found the presently claimed invention obvious over the broad disclosure of Del Soldato. Further, as claim 7 encompasses an "enantiomeric

excess of the (S) form higher than or equal to 98%" (emphasis added), Applicants submit that claim 7 is patentable for at least the same reasons as claim 6. As noted above, the present invention is a selection over the "umbrella" coverage of Del Soldato, and represents a separately patentable invention. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 6-7 under 35 U.S.C. § 103(a) as unpatentable over Del Soldato.

In view of the amendments and remarks above, Applicants respectfully submit that this application is in condition for allowance and requests favorable action thereon. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this paper is not considered to be timely filed, Applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, referring to Attorney Docket No. **026220-00038**. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referencing Attorney Docket No. **026220-00038**.

Respectfully submitted,


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